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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/425,075 | 10/21/1999 | PRABHAKARA V. CHOUDARY | 480.97-1-(HV | 9044 |

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EXAMINER

HELMS, LARRY RONALD

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1642

DATE MAILED: 09/12/2003

45

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/425,075

Applicant(s)

CHOUDARY ET AL.

Examiner

Larry R. Helms

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 36-39 and 41-50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 36-39, 41-50 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 43
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Request for Continued Examination

1. The request filed on 7/9/03 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/425075 is acceptable and a RCE has been established. Claims 36-39, 41-50 are pending and are currently under prosecution. An action on the RCE follows.
2. Claims 36-39, 41-50 are under examination.
3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

Response to Arguments

4. The rejection of claims 36-39, 42-50 under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al (Proc. Natl. Acad. Sci. USA 85:8678-8682, 1988) and further in view of Cregg et al (Developments in Industrial Microbiology 29:33-41, 1988) and The Invitrogen 1997 Catalog (published 1/97, Yeast expression pages 14-17 and Master Catalog Amendment Notice for pPICZ vectors from 4/15/96) and Robinson et al (U.S. Patent 6,204,023, filed 6/6/95) is maintained.

The response filed 7/9/03 has been carefully considered but is deemed not to be persuasive. The response states that the declaration of James Trager supports previous arguments that there is no suggestion of a dual expression cassette vector for use in *Pichia* and there is no reasonable expectation of success provided by the

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references and the state of the art would lead a skilled person away from combining the cited references (see pages 5-6 of response). Specifically the response states that the examiner has interpreted "yeast" to mean a genus of microorganisms that encompasses *Pichia* and Robinson uses the terms "yeast" and "*S. cerevisiae*" interchangeably and at no time does Robinson define "yeast" as anything other than *S. cerevisiae* and the preferred host is *S. cerevisiae* and these assertions are supported by the declaration of Dr. Trager (see page 7 of response). The declaration of Dr. Trager has been carefully considered but is deemed not to be persuasive. The declaration states that one would not expect the term "yeast" to mean "*pichia*" as read into the Robinson reference and the term can encompass 25,000 species. In response to this argument, the term "yeast" can encompass *Pichia* and in fact does and one reading the art of the invitrogen catalog in combination with the cited references would have motivation to use the *Pichia* strain as well as the expression vectors described therein such as pPICZalpha (which is the exact vector that applicants used) for the expression of the antibody because of the benefits recited for the *Pichia* expression system catalog. In addition, Robinson specifically teaches heavy and light chains each attached to a promoter and terminator sequence (see column 16, lines 15-20) as constructed in applicants vector (see Figure 1 of the instant specification). Thus, it would have been obvious to construct the vector with dual cassettes in view of Robinson and the invitrogen catalog.

The response further states that the art would lead a skilled person away from combining the cited references and cites Pennell (Res. Immunol 1998, 149:599-603) and Holliger (Methods in Mol. Biol. 2002, 178:348-57). The response states that

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Pennell teach that "to our knowledge, there are no reports of proteins greater than 117 kDa being expressed in *P. pastoris*" (see page 8 of response). The response has been carefully considered but is deemed not to be persuasive. In response to this argument, the Invitrogen catalog cites a wide variety of proteins that have been expressed in *Pichia* and it appears that one, GP-120, is greater than 117 kDa (see page or section 14). In addition, there is nothing in the cited reference of Pennell or the prior art of record that excludes the expression of an antibody or a protein as large as an antibody, Pennell just acknowledge that to there knowledge larger proteins of 117 kDa have not been reported.

The response states that Holliger teach that "Because bicistronic expression works only poorly in *Pichia* (unlike *E. coli*), it is preferable to use single-chain antibody formats. Two chain Ab formats require that the two chains be cloned and transformed separately." Thus, Holliger therefore appears to say that single expression cassette vectors are required if expression of two different chains of an antibody is desired (see page 8 of response). In response to this argument, the citation is in a reference and it is unclear what is meant by the citation. The citation is from reference number 8 and cites expression of antibodies in eukaryotic cells. There is no scientific evidence provided in the response to warrant the need to use two separate vectors. In fact Dr. Trager in the declaration states that "Holliger, therefore, appears to say that single expression cassette vectors are required if expression of two different chains of an antibody is desired" (see page 7) and as such even Dr. Trager seems to indicate that there may be some ambiguity in this citation because it is not clear what Holliger means. In addition,

again there is no scientific evidence to support that a dual cassette vector would not work in Pichia. In fact the Holliger reference teaches that Pichia system has advantages of more efficient folding of multidomain and cysteine rich proteins (see page 350) of which antibodies have multidomains and are cysteine rich, thus antibodies would be an obvious choice for expression in Pichia.

In view of the teaching of Horwitz for production of an antibody in yeast and in view of the teaching of Robinson et al that dual expression cassettes can be used for antibody production and the invitrogen catalog which describes vectors for expression in Pichia at high levels and Cregg et al for teaching a yeast promoter, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

5. The rejection of claims 36-39, 41-50 under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al (PNAS 85:8678-8682, 1988) and further in view of Cregg et al (Developments in Industrial Microbiology 29:33-41, 1988) and The Invitrogen 1997 Catalog (published 1/97, Yeast expression pages 14-19 and Master Catalog Amendment Notice for pPICZ vectors from 4/15/96), Robinson et al (U.S. Patent 6,204,023, filed 6/6/95) and Vanderlaan et al (U.S. Patent 5,429,925, issued 7/4/95) is maintained.

The response filed 7/9/03 has been carefully considered but is deemed not to be persuasive. The response states that the forgoing discussion adequately addresses this rejection and Vanderlaan only discusses the anti-dioxin antibody. In response to

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this argument, the same response is appropriate for this rejection as that above and is maintained for the same reasons.


Conclusion

6. No claim is allowed.
7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D., whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.
8. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879


LARRY R. HELMS, PH.D.
PRIMARY EXAMINER